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Evaluation of the Reliability and Validity of the Crawford  
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14. ABSTRACT The objective of this study is to analyze the reliability and validity of a classification system to assess tibial dysplasia in neurofibromatosis type 1. Radiographs of the lower extremity were collected on 36 individuals with NF1 and tibial bowing. Each radiograph (AP and lateral) was scored as either type I, type IIA, type IIB, or type IIC by the author of the peer-reviewed published criteria of Crawford (Crawford AH and Schorry EK. 1999. <i>J Am Academy of Orthopaedic Surgeons</i> ; 7:217-230). Dr. Crawford scored 16 as type I, 8 as type IIA, 7 as type IIB, and 5 as type IIC. The same set of radiographs was sent to 27 consented volunteers in the radiology and orthopedic communities, and 21 provided a rating. Each volunteer was asked to re-classify the set of radiographs 3 months later to assess the test-retest reliability. 12 reviewers of the first set re-reviewed the radiographs as a second rating. The analyses are underway and being prepared for submission for publication.					
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## **INTRODUCTION**

Tibial dysplasia (TD) and pseudarthrosis represents a significant challenge to pediatric and orthopedic practitioners. Management is extremely difficult and many patients experience multiple unsuccessful surgical attempts and amputation. The severity of TD is highly variable and radiographic presentation has been hypothesized to predict eventual outcome. Adoption of a universal radiographic classification for TD would provide a consistent measure to assess treatment efficacy.

The Crawford radiographic classification for tibial dysplasia has been adopted by the orthopedic community, which classifies tibial radiographs into four types (Type I, IIA, IIB, and IIC). The reliability and validity of this classification system has not yet been tested.

Our objective is to analyze both the reliability and the validity of the Crawford radiologic classification of tibial dysplasia. Radiographs of patients with TD will be reviewed at a pediatric orthopedic hospital and classified into each of the 4 classification categories. The radiographic images will be reviewed and classified by 30 orthopedists and radiologists. Three months later, they will be re-reviewed to assess test-retest reliability. Validity will be assessed by comparing the pooled responses to the reading provided by an expert most familiar with the classification scheme.

The Crawford radiographic classification scheme may predict eventual outcome in patients with TD. Application of a predictive system of classification would allow for better clinical management and treatment strategies for TD. Results of this study may lead to modifications of the current classification scheme to enhance reliability.

## **BODY (based on statement of work outlined in the original proposal)**

### **Task 1. Plan Development (Month 1):**

- a. Train a research coordinator to identify potential radiographs at pediatric orthopedic hospital.
- b. Have conference call with investigators and collaborators to discuss plan and timeline.
- c. Assure compliance with USAMRMC and home institutional guidelines. We have already contacted the Institutional Review Board at our institution and the proposal was administratively reviewed and determined to be exempt from the Federal regulations governing human research (IRB#11386).

We compiled a team of study coordinators at the Shriners Intermountain Hospital in Salt Lake City and determined appropriate ways to identify and request xrays that had been compiled in the Department of Radiology. IRB approval was clarified from the University of Utah and telephone conference calls were completed to assure a timeline to collect the radiographs, have Dr. Crawford provide a rating, copy radiographs on to CDs for distribution to volunteers. A lead study coordinator, Heather Hanson, was identified to assume the responsibilities and duties of coordinating the mailings and collection of materials.

### **Task 2. Radiographic Collection and Selection (Months 1 and 2):**

- a. Request and obtain all radiographs of patients with the following codes: (pseudarthrosis of bone, pseudarthrosis of tibia, neurofibromatosis generalized, neurofibromatosis of tibia, and non-union of fracture).
- b. Review all radiographs obtained.
- c. Select radiographs with tibial dysplasia (antero-lateral tibial bowing with or without pseudarthrosis) that do not have poor quality, instrumentation, or another obvious osseous condition (i.e. osteogenesis imperfecta).

- d. Remove any identifiers.
- e. Give non-related sequential number to each film.
- f. Transfer radiographic images to electronic CD-ROM.

Radiographs were obtained for review by collaborators at the University of Utah; David Viskochil, David Stevenson, and John Carey. Of 56 individuals with NF1 who had radiographs provided by the Shriners Intermountain Radiology Department, 36 were selected for the review set. Identifiers were removed and labeled with a non-related sequential number between 1 and 542 before transfer to CD-ROM.

**Task 3. Radiographic Review (Months 3-7):**

- a. Compile diagnostic key of Crawford's classification sheet, and classification response sheet.
- b. Send CD-ROM of radiographs of the dysplastic tibias to Dr. Crawford to be classified in best-fit model into each of his 4 classification categories. By doing this, we are imposing a type of "gold standard." However, Dr. Crawford will not be included in the inter-rater classification.
- c. Have conference call with investigators and collaborators to compile list of radiologists and orthopedists for review of compiled CD-ROM.
- d. Send radiographic images on CD-ROM (with diagnostic key of Crawford's classification and a classification response sheet) to 30 orthopedists and radiologists for review and classification.

A diagnostic key of Crawford's classification sheet with classification response sheet was developed and is attached in the Appendix. Dr. Carey was the PI of the original IRB approval (University of Utah IRB#11386: Analysis of the Reliability, Validity, and Prognosis of the Crawford Classification of Congenital Tibial Dysplasia), and this was conveyed on the forms. Dr. Crawford provided his classification of the 36 radiographs. There were 16 with Type I (44%), 8 with Type IIA (22%), 7 with Type IIB (19%), and 5 with Type IIC (14%). A list of approximately 100 radiologists and orthopedists was compiled from the local and extended healthcare community, and we sent CD-ROMs with an invitation to participate in this study. From that mailing, 21 were returned with an initial rating.

A significant effort was devoted to the procedure in which the volunteers could be compensated for their time. The University of Utah policies required strict adherence to handling of payments that must conform to the IRS.

**Task 4. Re-evaluation of Radiographic Review (Months 7-10):**

- a. Enter data from first review into spreadsheet.
- b. Send same radiographic images, re-coded and randomly rearranged, 3 months after initial review to the same 30 orthopedists and radiologists for review and classification.

As ratings came back they were entered in a spreadsheet. A total of 27 volunteers agreed to participate in the study, and 21 completed the first rating. Of these 21, 10 requested compensation. The last date of first rating was June of 2007, as there was difficulty in having the volunteers return their respective ratings. This aspect of the study necessitated extension of the project on 2 separate occasions. With respect to the first rating, there were a total of 8 respondents collected in 2005, 10 in 2006, and 3 in 2007.

The radiographic images were re-coded, randomly arranged and sent back to each volunteer who returned a first rating 3 months after the initial rating was returned.

**Task 5. Data Analyses (Months 10-12):**

- a. Enter data from second review into spreadsheet.
- e. Have conference call with investigators and collaborators to review data.
- b. Perform statistical analysis of data.
- c. Prepare manuscript for publication and presentation.
- d. A final report will be written.

Scoresheets from the 2<sup>nd</sup> rating were entered onto the spreadsheet as they were returned. Of the 21 volunteers who provided the first rating, 12 returned a second rating. The last 2<sup>nd</sup> rating was returned at the end of March, 2007. Even with multiple reminders, we did not receive any additional 2<sup>nd</sup> ratings through the extended study period that ended 12/31/2007. There have been no additional submissions up to March 1<sup>st</sup>, 2008, which is the date we closed the study. Data analysis is now being performed, and when complete a manuscript will be submitted with appropriate acknowledgement to the Department of Defense NF Program.

## **KEY RESEARCH ACCOMPLISHMENTS**

We assembled a set of 36 lower extremity radiographs of tibial dysplasia in patients with NF1 from the Shriners Intermountain Hospital Radiology Department. Our review of these radiographs led to a realization that an example of a bone abnormality widely cited in the NF1 diagnostic criteria is wrong. The NIH Consensus Development Conference established a set of diagnostic criteria useful in establishing a diagnosis of NF1 in the vast majority of individuals with NF1 (*Archives of Neurology*, 45:575-578, 1988). One criterion is distinctive skeletal finding stated as follows, “a distinctive osseous lesion such as sphenoid wing dysplasia, or thinning of long bone cortex with or without pseudarthrosis”. Upon review of the 36 radiographs assembled for this study, we realized that the long bone cortex of bowed tibia in NF1 was thickened rather than thinned. This led to our publication that called for a revision of the criteria (Stevenson et al., 2007, *Genetics in Medicine* – see appended article). This article was a direct result of this study, and it includes 3 co-investigators and a consultant as authors. In addition, we have submitted another manuscript to the Journal of Pediatric Orthopedics entitled Analysis of Radiographic Characteristics of Anterolateral Bowing of the Lower Leg Prior to Fracture in Neurofibromatosis Type 1 (See Appendix). David Stevenson and David Viskochil presented similar posters at 2 meetings; the CTF NF Symposium in Park City in 2007 and the 37<sup>th</sup> International Sun Valley Workshop on Skeletal Biology in August of 2007. An abstract of this poster that was published in the Journal of Musculoskeletal and Neuronal Interactions in 2007 is provided in the appendix.

The final analyses are being completed and will lead to an additional manuscript detailing the initial ratings of 21 radiologists and orthopedists. These data are being compared to the “gold standard”, Dr. Alvin Crawford’s rating using the Crawford classification system.

## **CONCLUSIONS**

This project has been successful in its contribution to the understanding of tibial dysplasia in NF1. It has provided a conduit for ideas between investigators interested in NF1-related bone health issues. We have maintained collaborations with Dr. Crawford at the University of Cincinnati, and the manuscript will be submitted with co-authors from the Universities of Utah, Cincinnati, and British Columbia. It has also fostered a strong collaboration with the Shriners Intermountain Hospital in Salt Lake City.

## **APPENDIX**

### **Page 8**

Stevenson DA, Viskochil DH, Schorry EK, Crawford AH, D'Astous J, Murray KA, Friedman JM, Armstrong L, Carey JC. 2007. The use of anterolateral bowing of the lower leg in the diagnostic criteria for neurofibromatosis type 1. *Genet Med* 9:409-412

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Stevenson DA, Carey JC, Viskochil DH, Moyer-Mileur L, Salter H, Murray M, D'Astous J, Murray K. Analysis of Radiographic Characteristics of Anterolateral Bowing of the Lower Leg Prior to Fracture in Neurofibromatosis Type 1. submitted to the *Journal of Pediatric Orthopedics* in April, 2008.

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# The use of anterolateral bowing of the lower leg in the diagnostic criteria for neurofibromatosis type 1

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## Abstract

Neurofibromatosis type 1 is diagnosed clinically based on the presence of two of seven criteria developed by a panel of experts in 1987. The sixth criterion focuses on skeletal findings and is as

follows: “A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.” The wording for this criterion is misleading. In particular, “thinning of long bone cortex” is not the characteristic radiographic presentation, and no mention of long bone bowing is included. The distinctive clinical feature of long bone dysplasia in neurofibromatosis type 1 is anterolateral bowing of the lower leg (portion of the body delimited by the knee and ankle). The usual radiographic findings of long bone dysplasia in neurofibromatosis type 1 at first presentation, prior to fracture, are anterolateral bowing with medullary canal narrowing and cortical thickening at the apex of the bowing. We suggest that anterolateral bowing of the lower leg, with or without fracture or pseudarthrosis, is a more appropriate description of the primary finding that a clinician will use to fulfill the sixth diagnostic criterion for neurofibromatosis type 1. Clarification of this diagnostic criterion is important for the clinician and for research protocols. Appropriate interpretation will improve understanding of the natural history and pathophysiology of neurofibromatosis type 1.

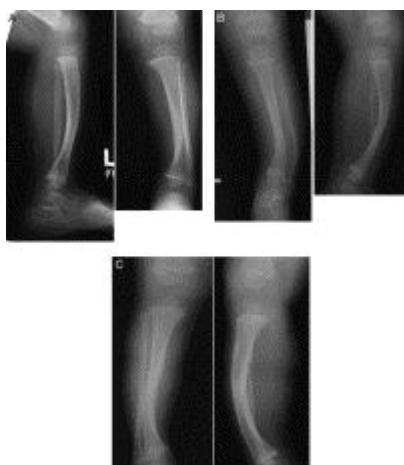
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Diagnostic criteria for neurofibromatosis type 1 (NF1) were established by a panel of experts at a National Institutes of Health (NIH) Consensus Development Conference in 1987.<sup>1</sup> A total of seven criteria were developed, and an individual must satisfy two of the seven criteria to fulfill the diagnosis of NF1. In 1997, members of the National Neurofibromatosis Foundation Clinical Care Advisory Board reviewed the available information and recommended a more comprehensive approach to the diagnosis and treatment of affected individuals, but no change in the NIH Diagnostic Criteria for NF1 was thought to be necessary at that time.<sup>2</sup>

The sixth criterion focuses on the distinctive skeletal findings of NF1. This criterion was stated as follows: “A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.”<sup>1</sup> Distinctive osseous lesions are uncommon in individuals with NF1 (3–5%),<sup>3</sup> and when this criterion was first established, in-depth knowledge of this manifestation was lacking. There is no doubt that a distinctive osseous lesion is an important diagnostic criterion in some individuals with NF1, but the standard statement of this criterion is misleading. Additionally, the example of “thinning of long bone cortex” is confusing because this is an unusual presentation of long bone dysplasia, especially in young children with NF1. As a consequence, some physicians have obtained radiographs of the legs, looking for the described “thinning of the cortex” in children whose physical examination does not show any focal skeletal abnormalities. Other physicians have raised concerns about how to quantify the “thin cortex” to fulfill this diagnostic criterion. Clearly, a better description of what constitutes a distinctive osseous lesion in NF1 is needed to use this sixth criterion more effectively.

Skeletal abnormalities associated with NF1 include scoliosis, sphenoid wing dysplasia, long bone dysplasia, bone cysts, and shorter than expected stature for familial background.<sup>4,5</sup> Probably the most characteristic skeletal abnormality observed in young children with NF1 is long bone dysplasia. The usual clinical presentation in infancy or early childhood is anterolateral bowing of the tibia, with the apex near the junction of the middle and distal thirds of the tibia ([Fig. 1](#)). In some cases, pathologic fracture occurs in the bowed region, and these fractures often do not heal normally, leading to nonunion or pseudarthrosis.<sup>4–6</sup> The terminology used to describe the clinical and radiographic findings is often confusing, and the skeletal abnormalities exist along a continuum. Most commonly, the characteristic long bone dysplasia of NF1 is incorrectly described as “congenital tibial pseudarthrosis,” although the process often involves the ipsilateral fibula as well and may affect the radius and/or ulna rather than the bones of the lower leg,<sup>6</sup> which we define as the portion of the body delimited by the knee and ankle. Reports of bowing and pseudarthrosis of the humerus and clavicle are rare but have also been published.<sup>7,8</sup>

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**Fig. 1.** Radiographs of the lower leg (both anteroposterior and lateral views) demonstrating anterolateral bowing of the tibia with cortical thickening (A–C).

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In addition, the term pseudarthrosis is clearly inappropriate when applied to a bone that has never fractured (or has fractured and healed adequately). Moreover, although anterolateral bowing of the lower leg is sometimes congenital and is usually recognized in infancy, fracture of a dysplastic tibia rarely occurs before birth. In addition, some individuals with unequivocal tibial dysplasia and anterolateral bowing do not fracture, and some who sustain a fracture heal adequately and do not develop pseudarthrosis. Therefore, the classic term *congenital tibial pseudarthrosis* used so often in the genetics and orthopedic literature is not the most appropriate term for this progressive process involving the long bones in individuals with NF1.

In 2000, the National Neurofibromatosis Foundation (now Children's Tumor Foundation) convened a task force on bone abnormalities in NF1 in Salt Lake City, UT, to discuss the natural history of long bone dysplasia and dysplastic scoliosis in NF1. Since that time, progress has been made in describing the clinical presentation, natural history, and radiographic findings of long bone bowing and pseudarthrosis in NF1.[4,6,9](#)

## **CHARACTERISTIC CLINICAL AND RADIOGRAPHIC FINDINGS IN NF1 PATIENTS WITH LONG BONE DYSPLASIA**

Anterolateral bowing of the lower leg, with the apex of the convexity near the junction of the middle and distal thirds of the tibia is the usual presenting clinical sign in an infant or child with long bone dysplasia characteristic of NF1. In some instances, fracture or pseudarthrosis has already occurred, but this is not always the case. Of note, pseudarthrosis without previous bowing of the long bone should be considered unrelated to NF1 unless other diagnostic criteria are satisfied.

Although some NF1 patients with tibial dysplasia do have thinning of the cortex on radiographic examination, most do not.[4,9](#) The most characteristic radiographic findings in a dysplastic tibia before fracture are cortical thickening with medullary canal narrowing that is greatest near the maximum point of bowing, usually located at the junction of the middle and distal thirds of the tibia ([Fig. 1](#)). Various other radiographic findings have also been observed in affected bones, including an increased width of the medullary canal with tubulation defects, cystic lesions, and a dysplastic constriction of the long bone.[10](#) In addition, osteopenia and cortical thinning at the very proximal and distal ends of the long bone can be seen after a fracture, but these abnormalities are probably secondary osseous changes that result from disuse.

Several radiographic classification systems have been proposed for tibial dysplasia, including the classifications of Boyd, Andersen, and Crawford.[4,10–21](#) It is, however, important to realize that 20% to 50% of individuals with tibial pseudarthrosis do *not* have NF1,[19,21,22](#) and some of the radiographic findings described in the various classification systems may represent features of conditions other than NF1. Other etiologies that have been suggested for tibial pseudarthrosis include intrauterine trauma, rickets, osteogenesis imperfecta, amniotic bands, fibrous dysplasia, and endocrine abnormalities.[23](#) In addition, some radiographic findings described in these classification systems may represent later stages of the disease, whereas other features may be typical of the findings at first presentation, before fracture, nonunion, or the effects of various treatments.[9](#)

Given that the radiographic findings are not static, it is important to consider what time period is most germane to the use of characteristic skeletal features as a diagnostic criterion for NF1. Cutaneous pigmentary, ocular, and tumor features of NF1 that are used as diagnostic features accumulate with

age.<sup>3,24</sup> Therefore, use of characteristic long bone dysplasia as a diagnostic criterion is most likely to be important in infancy or early childhood. At this time of life, tibial dysplasia is most likely to present as anterolateral bowing. In addition, cortical thickening rather than thinning is most likely to be observed radiographically. Regardless of the radiographic findings, clinical presentation of anterolateral bowing of the lower leg is probably adequate as a diagnostic criterion for NF1.

## **PROPOSED CLARIFICATION OF THE DIAGNOSTIC CRITERION**

The terminology of the example of a distinctive osseous lesion pertaining to long bone dysplasia currently used in the diagnostic criteria for NF1 is misleading for clinicians and researchers as a diagnostic criterion. Notably, long bone bowing, which is not mentioned as an example in the NF1 diagnostic criterion, is the primary clinical finding in long bone dysplasia. We propose to eliminate the example of “thinning of the cortex, with or without pseudarthrosis” used in the diagnostic criterion. If one were to use the example strictly as stated, relatively few NF1 individuals presenting with long bone bowing would meet this criterion. Anterolateral bowing of the lower leg, with or without fracture or pseudarthrosis, is the primary finding a clinician should use to fulfill the sixth diagnostic criterion for NF1.

The NF1 diagnostic criteria proposed in 1987 are well entrenched in medical practice for the clinical evaluation of individuals suspected to have NF1.<sup>1</sup> It is likely that most physicians in NF1 specialty clinics recognize the range of osseous features that are characteristic for NF1. Why is it important to clarify the diagnostic criterion related to characteristic osseous manifestations? In the absence of clinical bowing of the lower leg or leg pain, clinicians not familiar with NF1 may obtain radiographs and request cortical measurements to look for cortical thinning, although this is not clinically indicated. In addition, clinical recognition of anterolateral bowing as the cardinal sign of tibial dysplasia will facilitate early referral to an orthopedist for preventive and therapeutic strategies including bracing to avoid fracture and pseudarthrosis.<sup>4</sup> Also, the diagnostic criteria are important for appropriate inclusion in most clinical research protocols investigating NF1.

Parents of young children with isolated café-au-lait macules who do not yet fulfill the diagnostic criteria for NF1 may also be misled by the current terminology for the sixth diagnostic criterion. This is evidenced in literature circulated by national support groups for NF1. For example, a “Questions and Answers” pamphlet published by the Children's Tumor Foundation in 2005 states that one of the findings characterizing NF1 is “thinning of the shin bone.” It would be much more helpful to describe this finding as bowing of the lower leg toward the front and side of the body. Appropriate interpretation of the sixth diagnostic criterion should help to increase our understanding of the natural history and pathophysiology of NF1 and improve the clinical care of individuals with this condition.

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## **Analysis of Radiographic Characteristics of Anterolateral Bowing of the Lower Leg Prior to Fracture in Neurofibromatosis Type 1**

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## **Analysis of Radiographic Characteristics of Anterolateral Bowing of the Lower Leg Prior to Fracture in Neurofibromatosis Type 1**

### **Abstract**

**Background:** Anterolateral bowing of the lower leg with tibial pseudarthrosis is associated with neurofibromatosis type 1 (NF1) frequently leading to fracture and non-union. The objective of the study is to characterize the radiographic findings of tibial dysplasia in NF1.

**Methods:** Retrospective review of radiographs of tibial dysplasia from the Shriners Hospitals for Children, Salt Lake City over 52 years between 1950 and 2002, and peripheral quantitative computed tomography (pQCT) imaging of three individuals with anterolateral bowing of the leg without fracture compared to age- and gender-matched controls.

**Results:** NF1 individuals with bowing of the lower leg have subjectively thicker cortices with medullary narrowing on plain film radiographs. The pQCT images of NF1 individuals with anterolateral bowing show an unusual configuration of the tibia.

**Conclusions:** Individuals with NF1 who have anterolateral bowing of the lower leg have marked differences in tibial geometry.

**Clinical Relevance:** The characterization of the radiographic findings of long bone bowing in NF1 helps clarify the NF1 clinical diagnostic criteria.

### **Introduction**

NF1 is a common autosomal dominant condition due to mutations in the *NF1* gene.<sup>1</sup> The diagnosis of NF1 is typically based clinically on fulfillment of 2 out of 7 diagnostic criteria,<sup>2,3</sup> and one criteria focuses on the skeletal abnormalities associated with NF1. Long bone dysplasia is the prototypic skeletal manifestation of neurofibromatosis type 1 (NF1), with the tibia most commonly affected. The clinical

presentation of tibial dysplasia generally begins with anterolateral bowing of the lower leg. The bowed long bone typically progresses to fracture and non-union (pseudarthrosis).<sup>4,5</sup> Anterolateral bowing of the lower leg with subsequent pseudarthrosis is quite specific for NF1 and in and of itself should alert the physician to the potential diagnosis of NF1.

The NF1 diagnostic criterion for the skeletal abnormalities states: “A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.”<sup>2,3</sup> Our anecdotal clinical experience is that cortical thinning was not a consistent component of tibial dysplasia in NF1, resulting in discussion on clarification of this diagnostic criterion.<sup>6</sup> This prompted us to systematically investigate our clinical suspicions and better characterize the geometry of the tibia and fibula in individuals with NF1 with anterolateral bowing of the lower leg. In order to characterize the architecture of the lower leg in individuals with NF1, a retrospective review of radiographs of the lower leg of individuals with tibial dysplasia was performed. Additionally, a cross-sectional analysis of the lower leg of NF1 individuals with anterolateral bowing of the lower leg without fracture or surgery compared to healthy controls using peripheral quantitative computed tomography (pQCT), a modality that allows for the separation of the bone and muscle compartments with cross-sectional volumetric measurements, was performed.<sup>7</sup>

## **Materials and Methods**

### **Archived Radiograph Review**

Radiographs were obtained of the lower leg of patients with the following diagnostic codes: (pseudarthrosis of bone, pseudarthrosis of tibia, neurofibromatosis generalized, neurofibromatosis of the tibia, and non-union of fracture) at the Shriners Hospitals for Children, Salt Lake City over 52 years between 1950 and 2002. Radiographs with instrumentation or fracture of the tibia were excluded in attempt to more accurately assess the initial radiographic findings of tibial dysplasia. Radiographs in which the individual had a known genetic disorder besides NF1 were excluded. All eligible radiographs were reviewed by one pediatric radiologist (KM).  
Peripheral Quantitative Computed Tomography (pQCT)

*Patients:* Inclusion criteria for cases included: 1. clinical diagnosis of NF1 based on NIH diagnostic criteria;<sup>2,3</sup> 2. anterolateral bowing of the lower leg without fracture or surgical intervention. Individuals <4 years of age were excluded due to patient cooperation and pQCT machine limits for the ability of positioning based on leg length. NF1 individuals were recruited from an NF1 clinic and NF1 Registry at the University of Utah. Medical histories were obtained and physical examinations performed on all cases, and information such as orthopedic management, medication use, handedness, and pubertal maturation (determined by self-reported questionnaire using Tanner stage criteria<sup>8</sup>) was obtained. Controls were selected from a reference group of 474 healthy children without NF1 collected by the Center for Pediatric Nutrition Research at the University of Utah enrolled over the years 2000-2007 from the same geographic area.  
*Imaging Procedures (pQCT):* Cross-sectional slices of the affected leg(s) in individuals with NF1 and of the non-dominant leg in controls were measured by pQCT (XCT-2000; Stratec Medical Systems/Orthometrix, White Plains, NY) at relative distances of 4%, 38%, and 66% from the distal tibial growth plate. Dominance of the leg was based on self-reported handedness. The distal end of the medial malleolus and the internal point of

articulation at the knee were marked with an erasable pen. Distances between the two marks were measured in triplicate, and the two measurements within 2 mm of each other were averaged. The 4% distal tibial site was calculated by dividing 8 by the total length of the leg. Measurement of the 66% distal tibial site was obtained by calculating 66% of the average total length measurement of the leg and marked with erasable pen. Placing the non-dominant leg through the pQCT gantry, the pQCT laser was aligned with the distal reference mark (medial malleolus). A scout scan was performed to determine the position of the endplate and placement of the reference line in the distal tibia. The reference line was placed at the most proximal line to the distal growth plate or at the endplate if the growth plate was fused. Once the reference line was defined, the scanner automatically measured the calculated 4% and 38% distal tibial sites. Then the leg was manually slid back to the marked 66% distal tibial site and scanned. The 4% distal cross-section was used to determine trabecular vBMD (mg/cm<sup>3</sup>). The 38% and 66% distal cross-section was used to determine cortical vBMD and BMC as well as the bone geometric properties. Imaging was performed by a densitometry technologist certified by the International Society for Clinical Densitometry (HS).

Scans were analyzed utilizing XCT software. The 4% site analysis was based on 0.4 voxel size, with a threshold of 169 mg/cc, contour mode = 1, peel mode = 1, with the filter on. The 38% site analysis was based on 0.4 voxel size, with a cortical bone threshold of 711 mg/cc and cort mode = 1. The 66% site analysis was based on 0.8 voxel size, with a cortical threshold of 711 mg/cc and cort mode = 1.

#### Statistical Analyses:

*NF1 Individuals with Anterolateral Bowing of the Lower Leg:* In order to avoid secondary changes due to surgical manipulation or trauma, individuals with previous fracture and/or pseudarthrosis of the tibia were excluded. NF1 individuals were individually compared to selected age- and gender-matched controls, and Z-scores were generated.

## Results

### Archived Radiograph Review

A total of 24 cases with tibial bowing without fracture or instrumentation were identified from the archived radiographs available at the Shriners Hospitals for Children, Salt Lake City between 1950 and 2002. Anterolateral bowing was observed in 23/24 cases (one individual had posterolateral bowing). Subjectively, the cortex appeared thickened with medullary canal narrowing near the apex of the bowing in all 24 cases (see example in Fig. 1). The fibula was dysplastic in 20/24 cases. The apex of the bowing was most consistently located near the junction of the middle and distal thirds of the tibia. Gender was listed in 21 cases and 76% were male and 24% were female. We were unable to confirm if all of these individuals had a diagnosis of NF1 based on this retrospective review, but 16/24 individuals had a diagnosis of NF1 documented [(gender: 11 male; 4 female; 1 unknown); (fibula dysplastic 13/16)]. The individual with posterolateral bowing did not have a diagnostic code for NF1 listed.

### Peripheral Quantitative Computed Tomography (pQCT)

A total of 3 individuals with NF1 with anterolateral bowing of the lower leg without fracture or surgical intervention were identified and their clinical history, pQCT data, and analyses are reported individually:

Case #1: This 4-year-old boy has bilateral anterolateral bowing of the lower legs without fracture or surgical intervention. Bracing of both legs was started at approximately 10 months of age, which has continued since that time. Radiographs of the lower legs at 4 years of age show severe bilateral anterolateral bowing with cortical thickening with medullary canal narrowing at the apex of the bowing (Fig. 2A,B). The pQCT images confirm an unusual shape to the tibial cross-section with the appearance of a thickened cortex with medullary canal narrowing of both tibia when compared to an age- and gender-matched control (Fig. 2C,D,E). The Z-scores from pQCT values of each leg compared to the non-dominant leg of 7 healthy gender- and age-matched controls (age 3.5-4.5 years) are listed in Table I. When one compares the 38% distal tibial sites (Fig. 2C,D) to the radiographs (Fig. 2A,B) one notes that this is the pQCT region closest to the apex of the bowing on both legs. The Z-scores were higher for cortical thickness with a Z-score of +2.6 for the left leg, and +2.1 for the right leg, while the endosteal circumferences were lower with a Z-score of -1.2 and -2.4 respectively. In addition, the strength strain index was -1.3 for the left leg and -0.9 for the right leg.

Case #2: This 7-year-old boy has mild left anterolateral bowing of the lower leg. His clinical course has been relatively unremarkable without fracture. Bracing of the leg was intermittent with poor compliance from infancy to 5 years of age, and has since not worn the brace. Radiographs at 1 year of age show mild anterolateral bowing with subjective cortical thickening and medullary canal narrowing. Radiographs at 4 and 7 years of age show subjective improvement of the anterolateral bowing, cortical thickening, and medullary canal narrowing radiographically over time (Fig. 3A,B,C). Subjective evaluation of the pQCT images performed at 6 years of age does not reveal a striking change in the shape of the tibia (Fig. 3D) compared to an age- and gender-matched control (Fig. 3E). Upon comparison of the latest plain film radiograph (Fig. 3C) one observes only minimal residual bowing. The Z-scores from pQCT values of the affected left leg compared to the non-dominant leg of 20 healthy gender- and age-matched controls (age 5.5-6.5 years) are listed in Table I. At the 38% site, which again roughly correlates with the maximum area of bowing on plain film radiographs, the Z-scores were negative for all values except the cortical thickness which had a positive Z-score (Table I), although not as dramatic as the Z-scores observed in Case #1.

Case #3: This 17-year-old girl has left anterolateral bowing of the lower leg without fracture or surgical intervention. Bracing of the affected leg was started at 6 months of age and was used intermittently until approximately 13 years of age when bracing was discontinued. Upon comparison of previous serial radiographs the tibial appearance changed over time (Fig. 4A-F). The pQCT images show a dramatically altered configuration of the tibia, with the appearance of a flattened and elongated tibia upon cross-section (Fig. 4G) when compared to an age- and gender-matched control (Fig. 4H). The fibula also appears dysplastic (Fig. 4G). The z-scores from pQCT values of the affected left leg compared to the non-dominant leg of 21 healthy gender- and age-matched controls (age 5.5-6.5 years) are listed in Table I. There were no positive Zscores for any variable.

## Discussion

Based on our previous clinical experience, NF1 individuals with anterolateral bowing of the lower leg prior to fracture have medullary canal narrowing with cortical

thickening.<sup>6</sup> Our retrospective radiographic review confirmed the subjective appearance of cortical thickening with medullary canal narrowing near the apex of the bowing most consistently located near the junction of the middle and distal thirds of the tibia on plain films. The appearance of cortical thickening may be a response to the anterolateral bowing, as the cortex appears more thickened on the posterior concave aspect. Yet the bowing is typically present early in life before a significant amount of loading forces on the lower limb are placed, although one cannot discount prenatal forces and the strains from movement during infancy.

There may be a selection bias of radiographs selected, as we only included radiographs prior to fracture on our retrospective review, and it is likely that radiographic changes can develop after fracture and surgical manipulation. In addition, the radiographic findings may change with age as the bone remodels in response to mechanical strains and loading. Many individuals with early or more severe presentations may have fractured prior to radiographic imaging. In addition, bone is a 3-dimensional structure and plain radiographs cannot fully assess the geometry of the tibia. Our subjective opinion of cortical thickening and medullary canal narrowing on plain radiographs may be the result of rotational factors and cortical shadowing. Given that the analysis of the plain radiographs was a retrospective review, we cannot determine if all of the individuals had NF1. We were able to conclude that at least 67% (16/24) of the radiographic cases had a diagnosis of NF1 recorded, but it is likely that the majority of the remaining individuals also had NF1. The rationale for this assumption is based on a prospective Shriner Hospital cohort, in which 91% of individuals with tibial dysplasia had NF1 (unpublished data).

Of the 24 cases in which radiographs were retrospectively reviewed, there was an excess of males (76%) with tibial bowing. A previous study reported increased male gender with more surgeries and an earlier age of fracture in an international cohort of NF1 individuals with long bone dysplasia.<sup>4</sup> The increase in male gender reported by Stevenson et al.<sup>4</sup> was primarily due to the group of individuals with complications of fracture, pseudarthrosis, surgery, and/or amputation, and colleagues have postulated that the excess number of males was due to increased activity leading to the subsequent complications. However, in this report, the retrospective review of radiographs excluded those individuals with tibial fracture, pseudarthrosis, or surgical manipulation. Therefore, it appears that male gender may be a risk factor for anterolateral bowing of the tibia. Perhaps genetic modifiers located on the Y chromosome contribute to the development of tibial bowing.

Upon analysis of the pQCT data on the small number of individuals with anterolateral bowing without fracture or surgical intervention, the cortical thickness was increased at the 38% distal tibial site with a decrease in the endosteal circumference in Case #1 and #2. These findings are in concert with those observed on the retrospective review of plain radiographs, and support our recommendation to revise the example of long bone thinning in the NF1 diagnostic criterion.<sup>6</sup> However, the Z-scores for cortical thickness and endosteal circumference were decreased in Case #3. Even though there is an increase in the cortical thickness, the Strength Strain Index was decreased in these individuals with tibial and/or fibular dysplasia suggesting a potential risk of fracture with specific mechanical forces.

Upon subjective examination of the pQCT images at the 38% distal tibial site of the three individuals with anterolateral bowing, the tibia was abnormal with an unusual configuration. We question whether or not accurate numeric values using pQCT can be obtained when measurements used to calculate the values are based on a circle with equivalent bone area (“ring model”) if the tibia is abnormally shaped. It is also interesting that although the pQCT images were subjectively abnormal, each of the three cases had variable geometric findings.

The three NF1 individuals with anterolateral bowing of the lower leg in which pQCT images were performed had not, as of yet, sustained a fracture. The average age of fracture of NF1 individuals with anterolateral bowing of the lower leg is approximately 5 years of age.<sup>4</sup> Given the limitations of obtaining pQCT imaging in children <4 years of age due to machine limits based on leg length, there may be some bias in this cohort of NF1 individuals with tibial bowing as they had not yet sustained a fracture. Potentially, individuals who sustained a fracture and progressed to pseudarthrosis, who were younger, could have different pQCT values. In addition, we do not know if the herein reported individuals with anterolateral bowing of the lower leg will progress to fracture and nonunion.

Given that Case #1 is only 4-years-of-age he may be more likely to sustain a fracture and non-union compared to Case #2 and Case #3. Case #2 only had mild anterolateral bowing which seemed to improve over time and likely lies along the milder end of the phenotypic spectrum of tibial dysplasia. Case #3 is 17-years-of-age without a fracture and it is difficult to determine why she did not sustain a fracture previously. The bone modeling and remodeling based on intrinsic genetic factors and extrinsic forces on an anterolaterally bowed leg during her period of growth may have altered the tibial geometry from its original shape as it adapted over time. It is also possible that the geometric properties of the tibia in these three individuals have protective effects against fracture compared to other NF1 individuals with anterolateral bowing who progress to fracture. It is also likely that other genetic modifiers, in the context of a heterozygous *NF1* background, can affect long bone geometry differently. Prospective information will be useful to determine if any of the pQCT variables are prognostic indicators of fracture and pseudarthrosis.

Since bone is a dynamic organ that is constantly changing due to bone formation and resorption, it is reasonable to assume that therapeutic strategies could be directed to bone structure in individuals with NF1. The utilization of pQCT imaging may serve as an appropriate surrogate marker to assess the effects of bracing techniques, physical activity regimens, and pharmacologic targets in clinical trials for NF1 individuals with anterolateral bowing of the lower leg.

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## Legends

Fig. 1. Example of anterior-posterior (AP) and lateral radiographs of the lower leg of an individual with anterolateral bowing of the lower leg prior to fracture. Radiographs show subjective cortical thickening with medullary canal narrowing with apex of the anterolateral bowing located near the junction of the middle and distal thirds of the tibia

Fig. 2. Radiographs (AP and lateral views) of the right (A) and left (B) leg of Case #1 with bilateral anterolateral bowing at 4-years-of-age. The cortex appears thickened with medullary canal narrowing at the apex of the bowing bilaterally. (C,D) The pQCT images obtained at the 4%, 38% and 66% distal tibial site of the (C) left and (D) right leg at 4-years-of-age. The fibula also appears dysplastic. (E) PQCT images obtained at the 4%, 38% and 66% distal tibial site of the non-dominant leg of a healthy age- and gendermatched

control.

Fig. 3. Case #2: (A) Radiographs (AP and lateral views) of the left leg at 1-year-of-age. The cortex appears thickened with medullary canal narrowing at the apex of the bowing. (B) Repeat radiographs (AP and lateral views) of the left leg at 4-years-of-age. (C) Repeat radiographs (AP views) of the left leg at 7-years-of-age showing decreased lateral bowing with resolving cortical thickening and medullary canal narrowing. (D) The pQCT images obtained at the 4%, 38% and 66% distal tibial site of the left leg of Case #2 with left anterolateral bowing of the lower leg at 6-years-of-age. At the 38% distal tibial site, the cortex appears only mildly increased subjectively. (E) As a comparison, pQCT images obtained at the 4%, 38% and 66% distal tibial site of the non-dominant leg of a healthy age- and gender-matched control are provided.

Fig. 4. Radiographs (AP and lateral views) of the left leg in Case #3 with left anterolateral bowing at 7-months-of-age (A), 3-years-of-age (B), and 7-years-of-age. The cortex appears thickened with medullary canal narrowing at the apex of the bowing. Repeat radiograph (AP view) of the left leg at 13-years-of-age (D) shows straightening of the lateral bowing, but anterolateral bowing persists as shown by lateral radiographs at 15- and 16-years-of-age (E, F). (G) The pQCT images obtained at the 4%, 38% and 66% distal tibial site of Case #3 at 17-years-of-age. The fibula also appears dysplastic. (H) As a comparison, pQCT images obtained at the 4%, 38% and 66% distal tibial site of the non-dominant leg of a healthy age- and gender-matched control are provided.

### **Long Bone Dysplasia in Neurofibromatosis Type 1**

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**Objective:** Neurofibromatosis type 1 (NF1) is diagnosed clinically based on the presence of 2 of 7 criteria as developed by a panel of experts in 1987. The sixth criterion focuses on skeletal findings and is stated as follows: "A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis." The wording for this criterion is misleading. A better description of what constitutes a distinctive osseous lesion is needed to effectively use this sixth criterion.

**Methods:** We reviewed all radiographs of the lower leg of patients with the following diagnostic codes: (pseudarthrosis of bone, pseudarthrosis of tibia, neurofibromatosis generalized, neurofibromatosis of tibia, and non-union of fracture) at the Shriners Hospital for Children Intermountain over 52 years between 1950 and 2002. Radiographs with instrumentation or fracture of the tibia were excluded in order to assess the initial radiographic findings of tibial dysplasia. A total of 26 cases fitting the above criteria were identified.

**Results:** Anterolateral bowing was observed in 25/26 (one individual had posterolateral bowing). Cortical thickening near the apex of the bowing was observed in 27/27 individuals. The fibula was dysplastic in 21/26 individuals. The most characteristic radiographic findings in a dysplastic tibia prior to fracture are anterolateral bowing with medullary canal narrowing and cortical thickening that is greatest at the maximum point of bowing, usually located near the distal third of the tibia.

**Conclusions:** We propose to eliminate the example of "thinning of the cortex, with or without pseudarthrosis" used in the diagnostic criterion. We suggest that anterolateral bowing of the distal third of the leg, with or without fracture or pseudarthrosis, is a more appropriate description of the primary finding a clinician will use to fulfill the sixth diagnostic criterion for NF1. Clarification of this diagnostic criterion is important for the clinician and for research protocols utilizing these criteria for inclusion in therapeutic trials. Appropriate interpretation of these distinctive osseous lesions will improve understanding of the natural history and pathophysiology of NF1.